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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,607	01/30/2001	Ib Jonassen	4409-214-US	2082

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	17

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,607	JONASSEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-32 and 34-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-32 and 34-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/068,822* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 20-32 and 34-47 are pending.

Applicants' amendment filed December 9, 2002 (Paper No. 13) is acknowledged. Applicants' response has been fully considered. Claim 33 has been cancelled, claims 20 and 34 have been amended, and new claim 47 has been added. Therefore, claims 20-32 and 34-47 are examined.

Sequence Listing

2. A copy of Sequence Listing and a floppy disk containing the sequence listing filed April 8, 2003 (paper No. 15) are acknowledged, and CRF has been entered.

Objection Withdrawn

3. The previous objection to the specification and claim 33 regarding the [...] and "SEQ ID NO:" for a given sequence, is withdrawn in view of applicants' amendment to the specification and cancellation of the claim, and applicants' response at page 5 in Paper No. 13.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 20-26 and 34-40 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 6 in Paper No. 13.

5. The previous rejection of claims 25, 26, 39 and 40 under 35 U.S.C.112, second paragraph, regarding the lipophilic substituent contains an amino group, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 6 in Paper No. 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20-32 and 34-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2 or a specific GLP-1 analog having the same amino acid sequence as SEQ ID NO:2 with a lipophilic substituent attached to the C-terminal amino acid optionally via a spacer of Lys, Gly-Lys or Glu-Lys, does not reasonably provide enablement for a derivative of GLP-1 or an analog or fragment, or a derivative of GLP-2 or an analog or fragment, wherein the a lipophilic substituent optionally via a spacer is attached to the N-terminal or C-terminal amino acid of GLP-1 or GLP-2, where the sequences of GLP-1 or GLP-2 analogs or fragments are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 20-32 and 34-46 are directed to a derivative of GLP-1 or an analog or fragment (claims 20-32 and 47), or a derivative of GLP-2 or an analog or fragment (claims 34-46), wherein the a lipophilic substituent optionally via a spacer is attached to the N-terminal or C-terminal amino acid of GLP-1 or GLP-2. The specification, however, only discloses cursory conclusions (pages 2-5) without data supporting the findings, which state that the invention relates to the derivatives of peptide hormones such as GLP-1 or GLP-2 which have been modified by introducing lipophilic substituent comprising 8-40 carbon atoms in either the N-terminal or the C-terminal amino acid of the native peptide or analog thereof. There are no

indicia that the present application enables the full scope in view of the derivative of GLP-1 or GLP-2 analog containing the lipophilic substituent as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the analogs or fragments of GLP-1 or GLP-2 in the derivatives, and the effects of the derivatives in the treatment of diseases, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed variants for the derivatives except the derivative of GLP-1, SEQ ID NO:2 (page 6). The specification has not shown any derivatives of GLP-2 analogs being made or used.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Wagner *et al.*, WO 95/03405) indicates a recombinant polypeptide such as GLP-2 having modification at Nα-terminus or C-terminus produces a polypeptide is longer acting and more potent than the naturally occurring polypeptide; Muranishi *et al.* (J.

Controlled Release 19, 179-188 (1992)) teach three modified peptide hormones such as thyrotropin-releasing hormone, tetragastrin and insulin having the fatty acid moieties (acyl chains) attached to their N-termini. However, the prior art does not teach the modified GLP-1 or GLP-2 analog containing a lipophilic group, furthermore, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the GLP-1 or GLP-2 analogs or fragments in the derivatives containing the lipophilic group, and the effect of the derivative in treating various diseases to be considered enabling for the claimed variant.

(4). Predictability or unpredictability of the art:

The specification has shown one GLP-1 derivative, SEQ ID NO:2. However, the specification has not demonstrated the make and use of derivatives of GLP-1 or GLP-2 analogs, nor the effects of the derivatives, the invention is highly unpredictable regarding the effect of the derivative in the treatment of diseases.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to derivatives of GLP-1 or GLP-2 analogs or fragments containing lipophilic substituents attached to the N-terminal or C-terminal amino acid of GLP-1 or GLP-2 analogs. The specification indicates the derivatives of peptide hormones such as GLP-1 or GLP-2 which have been modified by introducing lipophilic substituent comprising 8-40 carbon atoms in either the N-terminal or the C-terminal amino acid of the native peptide or analog thereof (pages 2-5). However, the specification has not demonstrated the making and use of any derivatives of GLP-1 or GLP-2 analogs except for SEQ ID NO:2. There is no working

example demonstrating the effect of the derivative. Since the specification fails to provide sufficient teachings on the identities of various GLP-1 or GLP-2 analogs in the derivatives and the effect of the derivative in treating various diseases, it is necessary to carry out further experimentation to make the derivative and to assess the effect of the derivatives.

(6). Nature of the Invention

The scope of the claims encompasses derivatives of GLP-1 or GLP-2 analogs or fragments containing lipophilic substituents attached to the N-terminal or C-terminal amino acid of GLP-1 or GLP-2 analogs, but the specification does not demonstrate the make and the use of the derivative. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the art is unpredictable regarding the effects of claimed compound, and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the derivative.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20-32 and 34-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 20-32 and 34-47 are indefinite because of the use of the term "GLP-1 or analog or fragment thereof" or "GLP-2 or analog or fragment thereof". The term "GLP-1 or analog or fragment thereof" or "GLP-2 or analog or fragment thereof" renders the claim indefinite, it is

unclear what amino acid sequence the analog or fragment of GLP-1 or GLP-2 has, and whether the analog or fragment of GLP-1 or GLP-2 is functional or not. Claims 21-26, 28-32, 35-40 and 42-47 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

In response, applicants indicate the derivative differs from the parent compound by having a lipophilic substituent attached to the N- or C-terminus of the parent peptide via a spacer (pages 6-7 of the response). The argument is persuasive regarding the derivative, however, the applicants have not responded to the rejection on "analog or fragment thereof".

8. Claims 27-32 and 41-47 are indefinite because of the use of the term "Glu-Lys wherein the Lys is attached to the C-terminal amino acid or Asp-Lys wherein the Lys is attached to the C-terminal amino acid". The term cited renders the claim indefinite, it is unclear whether the Lys is attached to the C-terminal amino acid of the GLP-1 or Asp-Lys. Please insert a comma "," between "Glu-Lys wherein the Lys is attached to the C-terminal amino acid" and "or Asp-Lys wherein the Lys is attached to the C-terminal amino acid", without the comma, the claim reads Lys is attached to the C-terminal amino acid or Asp-Lys. Claims 28-32 and 42-47 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. Claims 27 and 41 are also indefinite because the claim recites Glu or Asp being as a spacer, and the lipophilic substituent being an acyl group of a fatty acid, it is not clear how Glu or Asp is attached to both the C-terminal amino acid and the lipophilic substituent, where the lipophilic substituent is an acyl group, but does not have an amino group.

In response, applicants indicate Lys in Glu-Lys or Asp-Lys is attached to the Glu or Asp and C-terminal amino acid. The argument is not found persuasive because the claim also reads Lys is attached to the C-terminal amino acid or Asp-Lys without the "," before "or" (see the section above).

9. Claim 47 is indefinite because SEQ ID NO:2 does not conform the limitation of claim 27. SEQ ID NO:2 has the Glu with the lipophilic substituent attached to N^{ε}-amino group of Lys, while the spacer Glu-Lys in claim 27 indicates Glu is connected to Lys via N^{α}-amino group.

Conclusions

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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June 26, 2003

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